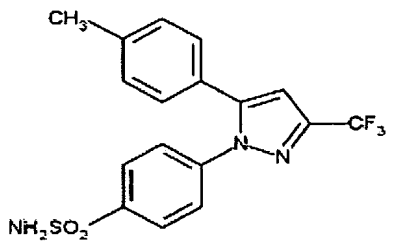
Celecoxib

From Wikipedia, the free encyclopedia

Celecoxib (INN) (IPA: [sɛlɛˈkɒksɪb]) is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis. It is marketed by Pfizer under the brand name **Celebrex**. In some countries, it is branded **Celebra**. Celecoxib is available by prescription in capsule form.

Contents



Celecoxib

Systematic (IUPAC) name

4-[5-(4-methylphenyl)-3-(trifluoromethyl) pyrazol-1-yl]benzenesulfonamide

Identifiers

CAS number	169590-42-5 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=169590-42-5&rn=1)
ATC code	L01XX33 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=L01XX33) M01AH01 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=M01AH01)
PubChem	2662 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2662)
DrugBank	APRD00373 (http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00373)

Chemical data

Formula	$C_{17}H_{14}N_3F_3O_2S$
Mol. weight	381.373 g/mol

Pharmacokinetic data

Bioavailability	?
Protein binding	97% (mainly to albumin)
Metabolism	Hepatic (mainly CYP2C9)
Half life	~11 hours
Excretion	Renal 27%, faecal 57%

Therapeutic considerations

Pregnancy cat.	B3 (Au)
Legal status	℞ Prescription only
Routes	Oral

Pharmacology

Celecoxib is a highly selective COX-2 inhibitor and primarily inhibits this isoform of cyclooxygenase, whereas traditional NSAIDs inhibit both COX-1 and COX-2. Celecoxib is approximately 10-20 times more selective for

COX-2 inhibition over COX-1. In theory, this specificity allows celecoxib and other COX-2 inhibitors to reduce inflammation (and pain) while minimizing gastrointestinal adverse drug reactions (e.g. stomach ulcers) that are common with non-selective NSAIDs.

Adverse effects

Main article: Non-steroidal anti-inflammatory drug

Celebrex, like all the other NSAIDs on the market, carries a boxed warning for cardiovascular and gastrointestinal risk.

Gastrointestinal ADRs

In theory the COX-2 selectivity should result in a significantly lower incidence of gastrointestinal ulceration than traditional NSAIDs. The main body of evidence touted to support this theory were the preliminary (6 month) results of the Celecoxib Long-term Arthritis Safety Study (CLASS) as published in 2000, which demonstrated a significant reduction in the combination of symptomatic ulcers plus ulcer complications in those taking celecoxib versus ibuprofen or diclofenac, provided they were not on aspirin (Silverstein *et al*, 2000). However, this was not significant at 12 months (full study length). It should be noted that this study used a very high dose of Celebrex, 800mg daily (400mg twice a day).

Allergy

Celecoxib contains a sulfonamide moiety and may cause allergic reactions in those allergic to other sulfonamide-containing drugs. This is in addition to the contraindication in patients with severe allergies to other NSAIDs.

History

Celecoxib was developed by G. D. Searle & Company and co-promoted by Monsanto (parent company of Searle) and Pfizer under the brand name Celebrex. Monsanto merged with Pharmacia, which was then acquired by Pfizer, giving Pfizer ownership of Celebrex. The drug was at the core of a major patent dispute that was resolved in Searle's favor (later Pfizer) in 2004. In *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004), the University of Rochester claimed that United States Pat. No. 6,048,850 (which claimed a method of inhibiting COX-2 in humans using a compound, without actually disclosing what that compound might be) covered drugs such as celecoxib. The court ruled in favor of Searle, holding in essence that the University had claimed a method requiring, yet provided no written description of, a compound that could inhibit COX-2 and therefore the patent was invalid.

After the withdrawal of rofecoxib (Vioxx) from the market in September 2004, Celebrex enjoyed a robust increase in sales. Then, in December 2004, one of two colon cancer prevention trials, named APC, found that long-term (33 months) of high-dose Celebrex (400 and 800mg daily) demonstrated an increased cardiovascular risk compared with placebo.[1] The other trial, named PreSAP, did not demonstrate an increased risk.[2] Still, the APC trial, combined with the Vioxx study, led to speculation that there is a cardiovascular risk for only the COX-2 drugs. However, a large Alzheimers prevention trial, called ADAPT, found that over-the-counter Aleve (naproxen) demonstrated an increased cardiovascular risk compared to placebo, whereas high-dose Celebrex (400mg daily) did not.[3]

Class Effect includes all NSAIDs, not just COX-2: In April 2005, after an extensive review of data and a 3-day Advisory Committee Meeting, the FDA concluded in its official memorandum: "we believe that it is reasonable to conclude that there is a 'class effect' for increased CV risk for all NSAIDs."[4] The FDA then mandated that all 18 prescription NSAIDs, including naproxen, ibuprofen, celebrex, diclofenac, etc, carry a boxed warning for cardiovascular risk. The FDA also published an NSAID medication guide for the public, which is available for free public download.[5] One interesting note for Celebrex is that no study has demonstrated an increased risk for heart attack or stroke when used at the approved dose for osteoarthritis: 200mg a day. A large observational study by David Graham of the Office of Drug Safety/FDA,[6] and a recent meta-analysis published in JAMA,[7] did not find an increased cardiovascular risk of Celebrex vs placebo. Neither of these studies were sponsored by a pharmaceutical company.

Still, it would be ideal if there could be a large, randomized trial that is specifically designed to measure cardiovascular events, as opposed to measuring colon cancer or Alzheimers disease. Pfizer has agreed to fund such a study, which will be directed by the Cleveland Clinic.[8] In this study that plans to enroll 20,000 high-risk patients, Celebrex will be compared to traditional anti-inflammatories (naproxen and ibuprofen), primarily to evaluate cardiovascular risk. Since all patients have arthritis, ethical considerations make it difficult to have a placebo group. This trial has just begun enrollment according to the Clinical Trials database, and is not scheduled to be completed until 2010. Ultimately, this trial will help answer the question as to whether Celebrex has a safer, riskier, or equal cardiovascular profile compared to naproxen or ibuprofen. Until then, the FDA guidelines remain the same: any NSAID, be it a non-selective NSAID such as naproxen or ibuprofen, as well as the COX-2 selective NSAID Celebrex, may increase cardiovascular risk.

Research into cancer prevention

The role that celecoxib might have in reducing the rates of certain cancers has been the subject of many studies. However, given the side effects of anti-COX-2 on rates of heart disease, there is no current medical recommendation to use this drug for cancer reduction.

- Colorectal cancer risk is clearly reduced in people regularly taking a NSAID like aspirin or celecoxib. In addition, some epidemiological studies, and most preclinical studies pointed out that specific COX-2 inhibitors like celecoxib are more potent and less toxic than "older" NSAIDs. Twelve carcinogenesis studies support that celecoxib is strikingly potent to prevent intestinal cancer in rats or mice (data avalaible on the Chemoprevention Database (http://www.inra.fr/reseau-nacre/sci-memb/corpet/indexan.html)). Small-scale clinical trials in very high risk people (belonging to FAP families) also indicate that celecoxib can prevent polyp growth. Hence large-scale randomized clinical trials were undertaken and results published by N.Arber and M.Bertagnolli in the New England Journal of Medicine, August 2006[1] (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16943400&dopt=Abstract) Results show a 33 to 45% polyp recurrence reduction in people taking 0.4-0.8 g celecoxib each day. However, serious cardiovascular events were significantly more frequent in the celecoxib treated groups (see above, cardiovascular toxicity).

References

- Malhotra S, Shafiq N, Pandhi P (2004). COX-2 inhibitors: a CLASS act or Just VIGORously promoted. *MedGenMed* **6** (1), 6. PMID 15208519 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15208519)
- Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al (2000). Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* **284** (10), 1247-55. PMID 10979111 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10979111)
- Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al (2005). Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* **352** (11), 1071-80. PMID 15713944 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15713944)

Footnotes

1. ^ Bertagnolli M, Eagle C, Zauber A, Redston M, Solomon S, Kim K, Tang J, Rosenstein R, Wittes J, Corle D, Hess T, Woloj G, Boisserie F, Anderson W, Viner J, Bagheri D, Burn J, Chung D, Dewar T, Foley T, Hoffman N, Macrae F, Pruitt R, Saltzman J, Salzberg B, Sylwestrowicz T, Gordon G, Hawk E (2006). "Celecoxib for the prevention of sporadic colorectal adenomas.". *N Engl J Med* **355** (9): 873-84. PMID 16943400 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16943400).
2. ^ Arber N, Eagle C, Spicak J, Rácz I, Dite P, Hajer J, Zavoral M, Lechuga M, Gerletti P, Tang J, Rosenstein R, Macdonald K, Bhadra P, Fowler R, Wittes J, Zauber A, Solomon S, Levin B (2006). "Celecoxib for the prevention of colorectal adenomatous polyps.". *N Engl J Med* **355** (9): 885-95. PMID 16943401 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16943401).
3. ^ ADAPT Research Group. Public Library of Science (PloS) Clinical Trials 2006;e33:1-10.
4. ^ Jenkins JK, Seligman PJ. (April 6, 2005). Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk [decision memorandum (http://www.fda.gov/cder/drug/infopage/cox2/NSAIDdecisionMemo.pdf)] (PDF). FDA Center for Drug Evaluation and Research.
5. ^ Medication Guide for Non-steroidal Anti-inflammatory Drugs (NSAIDs) (http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.pdf). FDA (June 15, 2005).
6. ^ Graham D, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray W (2005). "Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study.". *Lancet* **365** (9458): 475-81. PMID 15705456 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15705456).
7. ^ McGettigan P, Henry D (2006). "Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2.". *JAMA* **296** (13): 1633-44. PMID 16968831 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16968831).
8. ^ PRECISION : Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (http://clinicaltrials.gov/ct/show/NCT00346216?order=13). *ClinicalTrials.gov*. National Library of Medicine (December 7, 2006).

External links

- Celebrex website (http://www.celebrex.com/) run by Pfizer
- FDA Alert for Practitioners on Celebrex (celecoxib) (http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.htm), published 17 December 2004

- Largest systematic review of adverse renal and arrhythmia risk of Celecoxib and other COX-2 inhibitors, in JAMA 2006 (http://www.cox2drugreview.org/)
- Links to external chemical sources

Chemotherapeutic agents/Antineoplastic agents (L01) - Chemotherapy regimens	
Alkylating agents:	*Nitrogen mustards:* (Chlorambucil, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan). *Nitrosoureas:* (Carmustine, Fotemustine, Lomustine, Streptozocin). *Platinum:* (Carboplatin, Cisplatin, Oxaliplatin, BBR3464). Busulfan, Dacarbazine, Mechlorethamine, Procarbazine, Temozolomide, ThioTEPA, Uramustine
Antimetabolites:	*Folic acid:* (Aminopterin, Methotrexate, Pemetrexed, Raltitrexed). *Purine:* (Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Thioguanine). *Pyrimidine:* (Capecitabine, Cytarabine, Fluorouracil, Gemcitabine)
Plant alkaloids:	*Taxane:* (Docetaxel, Paclitaxel). *Vinca:* (Vinblastine, Vincristine, Vindesine, Vinorelbine).
Cytotoxic/antitumor antibiotics:	*Anthracycline family:* (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone, Valrubicin). Bleomycin, Hydroxyurea, Mitomycin
Topoisomerase inhibitors:	Topotecan, Irinotecan, *Podophyllum:* (Etoposide, Teniposide).
Monoclonal antibodies:	Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Panitumumab, Rituximab, Tositumomab, Trastuzumab
Photosensitizers:	Aminolevulinic acid, Methyl aminolevulinate, Porfimer sodium, Verteporfin
Kinase inhibitors:	Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Nilotinib, Sorafenib, Sunitinib, Vandetanib (ZD6474)
Other:	Alitretinoin, Altretamine, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Bexarotene, Bortezomib, Denileukin diftitox, Estramustine, Hydroxycarbamide, Pentostatin, Masoprocol, Mitotane, Pegaspargase, Tretinoin

Categories: Non-steroidal anti-inflammatory drugs | Pyrazoles

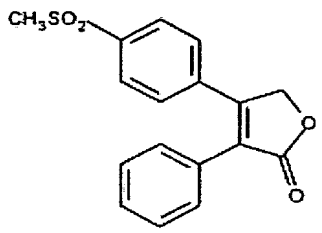
Rofecoxib

From Wikipedia, the free encyclopedia
(Redirected from Vioxx)

Rofecoxib (IPA: [rofə'kɒksɪb]) is a nonsteroidal anti-inflammatory drug (NSAID) developed by Merck & Co. to treat osteoarthritis, acute pain conditions, and dysmenorrhoea. Rofecoxib was approved as safe and effective by the Food and Drug Administration (FDA) on May 20, 1999 and was subsequently marketed under the brand name **Vioxx®**, **Ceoxx®** and **Ceeoxx®**.

Rofecoxib gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, over 80 million people were prescribed rofecoxib at some time.

On September 30, 2004, Merck voluntarily withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal, Merck had sales revenue of US$2.5 billion from Vioxx.



Rofecoxib

Systematic (IUPAC) name	
	4-(4-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one
Identifiers	
CAS number	162011-90-7 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=162011-90-7&rn=1)
ATC code	M01AH02 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=M01AH02)
PubChem	5090 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5090)
DrugBank	APRD00151 (http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00151)
Chemical data	
Formula	$C_{17}H_{14}O_4S$
Mol. weight	314.357 g/mol
Pharmacokinetic data	
Bioavailability	93%
Protein binding	87%
Metabolism	hepatic
Half life	17 hours
Excretion	biliary/renal
Therapeutic considerations	
Pregnancy cat.	C (Australia)
Legal status	*withdrawn*
Routes	oral

Rofecoxib was available on prescription as tablets and as an oral suspension.

Contents

The COX Enzyme

In the early 1990s, scientists discovered that the COX enzyme had two forms, now called COX-1 and COX-2. COX-1 mediated the synthesis of prostaglandins responsible for protection of the stomach lining, while COX-2 mediated the synthesis of prostaglandins responsible for pain and inflammation. By creating "selective" NSAIDS that inhibit COX-2, but not COX-1, scientists hypothesized they could offer the same pain relief as traditional NSAIDS, but with greatly reduced risk of fatal or debilitating peptic ulcers.

Rofecoxib is a selective COX-2 inhibitor or coxib (CycloOXygenase-2 InhiBitors). Others include Pfizer's celecoxib (Celebrex) and valdecoxib (Bextra). Interestingly, at the time of its withdrawal, rofecoxib was the only coxib with clinical evidence of its superior gastrointestinal adverse effect profile over conventional NSAIDs. This was largely based on the VIGOR (Vioxx GI Outcomes Research) study, which compared the efficacy and adverse effect profiles of rofecoxib and naproxen. (Bombardier *et al.*, 2000).

Adverse drug reactions

Main article: Non-steroidal anti-inflammatory drug

Aside from the reduced incidence of gastric ulceration, rofecoxib exhibits a similar adverse effect profile to other NSAIDs. Rofecoxib, however, does appear to increase the risk of adverse cardiovascular events (see below).

The chief mechanism proposed to explain rofecoxib's cardiotoxicity is the suppression of prostaglandin, an anti-clotting agent in the blood (Fitzgerald, 2004). COX-2 plays a role in the production of prostaglandin. Because Vioxx inhibits the COX-2 enzyme, prostaglandin production can decrease in endothelial cells and lead to an inefficiency in declumping and vasorelaxtion. Merck, however, argues that

there was no effect on prostaglandin production in blood vessels in animal testing.[1] (http://www.sfgate.com/cgi-bin/article.cgi?f=/n/a/2006/02/14/financial/f124814S66.DTL&type=health) Other researchers have speculated that the cardiotoxicity may be associated with maleic anhydride metabolites formed when rofecoxib becomes ionised under physiological conditions. (Reddy & Corey, 2005)

Vioxx has also been associated with cardiovascular disease, renal (kidney) disease, and heart arrhythmia.

Withdrawal from the market

VIGOR study

The VIGOR (Vioxx GI Outcomes Research) study, which compared the efficacy and adverse effect profiles of rofecoxib and naproxen. (Bombardier *et al.*, 2000), had indicated a significant 4-fold increased risk of acute myocardial infarction (heart attack) in rofecoxib patients when compared with naproxen patients (0.4% vs 0.1%, RR 0.25) over the 12 month span of the study. The elevated risk began during the second month on rofecoxib. There was no significant difference in the mortality from cardiovascular events between the two groups. Nor was there any significant difference in the rate of myocardial infarction between the rofecoxib and naproxen treatment groups in patients without high cardiovascular risk. The difference in overall risk was accounted for by the patients at higher risk of heart attack: those meeting the criteria for low-dose aspirin prophylaxis of secondary cardiovascular events (previous myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, or coronary artery bypass). (Bombardier *et al.*, 2000)

Merck's scientists interpreted the finding as a protective effect of naproxen, telling the FDA that the difference in heart attacks "is primarily due to" this protective effect (Targum, 2001 (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf)). Some commentators have noted that naproxen would have to be three times as effective as aspirin to account for all of the difference (Michaels 2005 (http://www.powerlinefacts.com/Sciam_article_on_lobbying.htm)), and some outside scientists warned Merck that this claim was implausible before VIGOR was published [2] (http://www.saferdrugsnow.org/documents/vio/E-mailreCarloPatronoVIGOR.pdf). No evidence has since emerged for such a large cardioprotective effect of naproxen, although a number of studies have found protective effects similar in size to those of aspirin (Karha and Topol, 2004; Solomon *et al.*, 2002). Though Dr. Topol's 2004 paper criticized Merck's naproxen hypothesis, he himself co-authored a 2001 JAMA article stating "because of the evidence for an antiplatelet effect of naproxen, it is difficult to assess whether the difference in cardiovascular event rates in VIGOR was due to a benefit from naproxen or to a prothrombotic effect from rofecoxib." (Mukherjee, Nissen and Topol, 2001.)

The results of the VIGOR study were submitted to the United States Food and Drug Administration (FDA) in February 2001, which led to the introduction, in April 2002, of warnings on Vioxx labelling concerning the increased risk of cardiovascular events (heart attack and stroke).

NEJM controversy

Months after the preliminary version of VIGOR was published in the New England Journal of Medicine, the journal editors learned that certain data reported to the FDA was not included in the NEJM article. Several years later, when they were shown a Merck memo during the depositions for the first federal

Vioxx trial, they realized that this data had been available to the authors months before publication. The editors wrote an editorial accusing the authors of deliberately withholding the data (Curfman et al, 2006a (http://content.nejm.org/cgi/content/extract/353/26/2813)). They released the editorial to the media on December 8, 2005, before giving the authors a chance to respond. NEJM editor Gregory Curfman explained that the quick release was due to the imminent presentation of his deposition testimony, which he feared would be misinterpreted in the media. He had earlier denied any relationship between the timing of the editorial and the trial. Although his testimony was not actually used in the December trial, Curfman had testified well before the publication of the editorial.[3] (http://www.forbes.com/work/feeds/ap/2006/02/13/ap2523250.html)

The editors charged that "more than four months before the article was published, at least two of its authors were aware of critical data on an array of adverse cardiovascular events that were not included in the VIGOR article." This additional data included three additional heart attacks, and raised the relative risk of Vioxx from 4.25-fold to 5-fold. All the additional heart attacks occurred in the group at low risk of heart attack (the "aspirin not indicated" group) and the editors noted that the omission "resulted in the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups." The relative risk for myocardial infarctions among the aspirin not indicated patients increased from 2.25 to 3 (although it remained statitistically insignificant). The editors also noted a statistically significant (2-fold) increase in risk for serious thromboembolic events for this group, an outcome that Merck had not reported in the NEJM, though it had disclosed that information publicly in March 2000, eight months before publication. (Curfman et al., 2006b (http://content.nejm.org/cgi/content/extract/354/11/1193), Supplementary Material).

The authors of the study, including the non-Merck authors, responded by claiming that the three additional heart attacks had occurred after the prespecified cutoff date for data collection and thus were appropriately not included. (Utilizing the prespecified cutoff date also meant that an additional stroke in the naproxen population was not reported.) Furthermore, they said that the additional data did not qualitatively change any of the conclusions of the study, and the results of the full analyses were disclosed to the FDA and reflected on the Vioxx warning label. They further noted that all of the data in the "omitted" table was printed in the text of the article. The authors stood by the original article. (Bombardier et al., 2006 (http://content.nejm.org/cgi/content/abstract/NEJMc066096)).

NEJM stood by its editorial, noting that the cutoff date was never mentioned in the article, nor did the authors report that the cutoff for cardiovascular adverse events was before that for gastrointestinal adverse events. The different cutoffs increased the reported benefits of Vioxx (reduced stomach problems) relative to the risks (increased heart attacks). (Curfman et al., 2006b (http://content.nejm.org/cgi/content/extract/354/11/1193)).

Some scientists have accused the NEJM editorial board of making unfounded accusations.[4] (http://pipeline.corante.com/archives/2006/02/22/nejm_vs_its_contributors_round_two.php), [5] (http://dimer.tamu.edu/simplog/archive.php?blogid=3&pid=3293) Others have applauded the editorial. Renowned research cardiologist Eric Topol [6] (http://genetics.case.edu/faculty2.php?fac=ejt9), a prominent Merck critic, accused Merck of "manipulation of data" and said "I think now the scientific misconduct trial is really fully backed up" [7] (http://www.medicinenet.com/script/main/art.asp?articlekey=56384&page=2). Phil Fontanarosa, executive editor of the prestigious Journal of the American Medical Association, welcomed the editorial, saying "this is another in the long list of recent examples that have generated real concerns about trust and confidence in industry-sponsored studies" [8]

(http://www.beasleyallen.com/news/2005/dec/10/article/510/).

Alzheimer's studies

In 2000 and 2001, Merck conducted several studies of rofecoxib aimed at determining if the drug slowed the onset of Alzheimer's disease. Merck has placed great emphasis on these studies on the grounds that they are relatively large (almost 3000 patients) and compared rofecoxib to a placebo rather than to another pain reliever. These studies found an elevated death rate among rofecoxib patients, although the deaths were not generally heart-related. However, they did not find any elevated cardiovascular risk due to rofecoxib (Konstam *et al.*, 2001). Before 2004, Merck cited these studies as providing evidence, contrary to VIGOR, of rofecoxib's safety.

APPROVe study

In 2001, Merck commenced the APPROVe (Adenomatous Polyp PRevention On Vioxx) study, a three year trial with the primary aim of evaluating the efficacy of rofecoxib for the prophylaxis of colorectal polyps. Celecoxib had already been approved for this indication, and it was hoped to add this to the indications for rofecoxib as well. An additional aim of the study was to further evaluate the cardiovascular safety of rofecoxib.

The APPROVe study was terminated early when the preliminary data from the study showed an increased relative risk of adverse thrombotic cardiovascular events (including heart attack and stroke), beginning after 18 months of rofecoxib therapy. In patients taking rofecoxib, versus placebo, the relative risk of these events was 1.92 (rofecoxib 1.50 events vs placebo 0.78 events per 100 patient years). The results from the first 18 months of the APPROVe study did not show an increased relative risk of adverse cardiovascular events. Moreover, overall and cardiovascular mortality rates were similar between the rofecoxib and placebo populations. (Bresalier *et al.*, 2005)

In sum, the APPROVe study suggested that long-term use of rofecoxib resulted in nearly twice the risk of suffering a heart attack or stroke compared to patients receiving a placebo.

Other studies

Pre-approval Phase III clinical trials, like the APPROVe study, showed no increased relative risk of adverse cardiovascular events for the first eighteen months of rofecoxib usage (Merck, 2004). Others have pointed out that "study 090," a pre-approval trial, showed a 3-fold increase in cardiovascular events compared to placebo, a 7-fold increase compared to nabumetone (another [NSAID]), and an 8-fold increase in heart attacks and strokes combined compared to both control groups [9] (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf) [10] (http://content.nejm.org/cgi/content/full/351/27/2875#T1). Although this was a relatively small study and only the last result was statistically significant, critics have charged that this early finding should have prompted Merck to quickly conduct larger studies of Merck's cardiovascular safety. Merck notes that it had already begun VIGOR at the time Study 090 was completed. Although VIGOR was primarily designed to demonstrate new uses for rofecoxib, it also collected data on adverse cardiovascular outcomes.

Several very large observational studies have also found elevated risk of heart attack from rofecoxib. For example, a recent retrospective study of 113,000 elderly Canadians suggested a borderline statistically

significant increased relative risk of heart attacks of 1.24 from Vioxx usage, with a relative risk of 1.73 for higher-dose Vioxx usage. (Levesque, 2005). Another study, using Kaiser Permanente data, found a 1.47 relative risk for low-dose Vioxx usage and 3.58 for high-dose Vioxx usage compared to current use of celecoxib, though the smaller number was not statistically significant, and relative risk compared to other populations was not statistically significant. (Graham, 2005).

Furthermore, a more recent study of 114 randomized trial comprised of 116,000+ participants, published in JAMA, showed that Vioxx uniquely increased risk of renal (kidney) disease, and heart arrhythmia. COX-2 Inhibitor Drug Review of adverse renal and arrhythmia risk, in JAMA 2006 (http://www.cox2drugreview.org/)

Withdrawal

Merck publicly announced its voluntary withdrawal of the drug from the market worldwide on September 30, 2004.

In addition to its own studies, on September 23, 2004 Merck apparently received information about new research by the FDA that supported previous findings of increased risk of heart attack among rofecoxib users (Grassley, 2004). FDA analysts estimated that Vioxx caused between 88,000 and 139,000 heart attacks, 30 to 40 percent of which were probably fatal, in the five years the drug was on the market.

On November 5 the medical journal *The Lancet* published a meta-analysis of the available studies on the safety of rofecoxib (Jüni *et al.*, 2004). The authors concluded that, owing to the known cardiovascular risk, rofecoxib should have been withdrawn several years earlier. *The Lancet* published an editorial which condemned both Merck and the FDA (http://thelancet.com/journal/vol364/iss9446/full/llan.364.9446.early_online_publication.31178.1) for the continued availability of rofecoxib from 2000 until the recall. Merck responded by issuing a rebuttal of the Jüni *et al.* meta-analysis that noted that Juni omitted several studies that showed no increased cardiovascular risk. (Merck & Co., 2004).

In 2005, advisory panels in both the U.S. and Canada encouraged the return of rofecoxib to the market, stating that rofecoxib's benefits outweighed the risks for some patients. The FDA advisory panel voted 17-15 to allow the drug to return to the market despite being found to increase heart risk. The vote in Canada was 12-1, and the Canadian panel noted that the cardiovascular risks from rofecoxib seemed to be no worse than those from ibuprofen[11] (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/cox2/sap_summary_gcs_sommaire_cox2_e.html) -- though the panel recommended that further study was needed for all NSAIDs to fully understand their risk profiles. Notwithstanding these recommendations, Merck has not returned rofecoxib to the market.

Litigation

As of March 2006, there had been over 10,000 cases and 190 class actions filed against Merck over adverse cardiovascular events associated with rofecoxib and the adequacy of Merck's warnings. The first wrongful death trial, *Rogers v. Merck*, was scheduled in Alabama in the spring of 2005, but was postponed after Merck argued that the plaintiff had falsified evidence of rofecoxib use.[12] (http://www.nytimes.com/2005/04/13/business/13drug.html?ex=1271044800&en=3225bb00e74eab08&ei=5090&partner=rssuserland)

On August 19, 2005, a jury in Texas voted 10-2 to hold Merck liable for the death of Robert Ernst, a 59-year old man who allegedly died of a rofecoxib-induced heart attack. The plaintiffs' lead attorney was Mark Lanier. Merck argued that the death was due to cardiac arrhythmia, which had not been shown to be associated with rofecoxib use. The jury awarded Carol Ernst, widow of Robert Ernst, $253.4 million in damages. This award will almost certainly be capped at no more than USD$26.1 million because of punitive damages limits under Texas law.[13] (http://www.msnbc.msn.com/id/9006921/) As of March 2006, the plaintiff had yet to ask the court to enter a judgment on the verdict; Merck has stated that it will appeal.

On November 3, 2005, Merck won the second case *Humeston v. Merck*, a personal injury case, in Atlantic City, New Jersey. The plaintiff experienced a mild myocardial infarction and claimed that rofecoxib was responsible, after having taken it for two months. Merck argued that there was no evidence that rofecoxib was the cause of Humeston's injury and that there is no scientific evidence linking rofecoxib to cardiac events with short durations of use. The jury ruled that Merck had adequately warned doctors and patients of the drug's risk.[14] (http://www.npr.org/templates/story/story.php?storyId=4988532)

The first federal trial on rofecoxib, *Plunkett v. Merck*, began on November 29, 2005 in Houston, Texas. The trial ended in a hung jury and a mistrial was declared on December 12, 2005. According to the *Wall Street Journal*, the jury hung by an eight to one majority, favoring the defense. Upon retrial in February 2006 in New Orleans, Louisiana, where the Vioxx multi-district litigation (MDL) is based, a jury found Merck not liable, even though the plaintiffs had the NEJM editor testify as to his objections to the VIGOR study.

On January 30, 2006, a New Jersey state court dismissed a case brought by Edgar Lee Boyd, who blamed Vioxx for gastiointestinal bleeding that he experienced after taking the drug. The judge said that Boyd failed to prove the drug caused his stomach pain and internal bleeding.

In January 2006, *Garza v. Merck* began trial in Rio Grande City, Texas. The plaintiff, a 71-year-old smoker with heart disease, had a fatal heart attack three weeks after finishing a one-week sample of rofecoxib. On April 21, 2006 the jury awarded the plaintiff $7 million compensatory and $25 million punitive. The punitive amount will be reduced to under $1 Million.

On April 5, 2006, the jury held Merck liable for the heart attack of 77-year-old John McDarby, and awarded Mr McDarby $4.5 million in compensatory damages based on Merck's failure to properly warn of Vioxx safety risks. After a hearing on April 11, 2006, the jury also awarded Mr McDarby an additional $9 million in punitive damages. The same jury found Merck not liable for the heart attack of 60-year-old Thomas Cona, a second plaintiff in the trial.

Merck has reserved $970 million to pay for its Vioxx-related legal expenses through 2007.

Merck sales representatives are now being subpoenaed to court over selling Vioxx to doctors- patients are claiming the reps knew of the side effects and are partially responsible for the wrongful deaths.

Political impact of Vioxx litigation in America

The recall and litigation over rofecoxib has provoked debate over drug safety in the United States. Some argue that the U.S. Food and Drug Administration does not do enough to monitor product safety and that

the rofecoxib withdrawal is an argument against tort reform. It has also been argued that litigation is an imperfect means of regulation that would overdeter companies for complying with FDA requirements, and that large awards like that in *Ernst* would inhibit research and development.

Other COX-2 inhibitors

It is currently unknown whether the increased risk of adverse cardiovascular events is common to all COX-2 inhibitors. Recent studies have demonstrated the increased risk of cardiovascular events associated with the use of celecoxib (Celebrex), valdecoxib (Bextra) and parecoxib (Dynastat). (Solomon *et al.*, 2005; Nussmeier *et al.*, 2005)

Newer and more specific COX-2 inhibitors, including etoricoxib (Arcoxia) and lumiracoxib (Prexige), are currently (circa 2005) undergoing Phase III/IV clinical trials. It is likely that these trials will be extended in order to supply additional evidence of cardiovascular safety.

A recent systematic review of 114 clinical trials, published in JAMA 2006, evaluated the adverse renal (kidney) and arrhythmia risks of celecoxib, valdecoxib, parecoxib, lumiracoxib, and etoricoxib. COX-2 Inhibitor Drug Review of adverse renal and arrhythmia risk, in JAMA 2006 (http://www.cox2drugreview.org/)

Regulatory authorities worldwide now require warnings about cardiovascular risk of COX-2 inhibitors still on the market. For example, in 2005, EU regulators required the following changes to the product information and/or packaging of all COX-2 inhibitors (EMEA 2005 (http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf)):

- Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

Miscellaneous

- Rofecoxib was shown to improve premenstrual acne vulgaris in a placebo controlled study.[15] (http://bioline.utsc.utoronto.ca/archive/00002693/01/dv04120.pdf#search=%22acne%20rofecoxib%22)

References

- Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, *et al.*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;**343**(21): 1520-8. PMID 11087881 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11087881)
- Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, *et al.* Cardiovascular

events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;**352**(11): 1092-102. PMID 15713943 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15713943)

- Curfman GD, Morrissey S, and Drazen JM. Expression of Concern Reaffirmed. *N Engl J Med* 2006; published online February 22. PMID 16495386 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16495386)
- EMEA (2005) European Medicines Agency, "European Medicines Agency concludes action on COX-2 inhibitors," press release, June 27, 2005. Link (http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf)
- FDA (2005). "Summary minutes for the February 16, 17 and 18, 2005, Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee." Published on the internet, March 2005. Link (http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4090M1_Final.htm)
- Fitzgerald GA, Coxibs and Cardiovascular Disease, *N Engl J Med* 2004;**351**(17): 1709-1711. PMID 15470192 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15470192).
- Grassley CE (15 Oct 2004). *Grassley questions Merck about communication with the FDA on Vioxx. (http://finance.senate.gov/press/Gpress/2004/prg101504.pdf)* Press Release.
- Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M (2004). Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. (http://image.thelancet.com/extras/04art10237web.pdf) *Lancet* (published online)
- Karha J and Topol EJ. The sad story of Vioxx, and what we should learn from it (http://www.ccjm.org/PDFFILES/Karha12_04.pdf) *Cleve Clin J Med* 2004; **71**(12):933-939. PMID 15641522 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15641522)
- M. A. Konstam *et al.*, "Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib," Circulation 104 (2001): 2280–2288
- Michaels, D. (June 2005) DOUBT Is Their Product (http://www.powerlinefacts.com/Sciam_article_on_lobbying.htm), *Scientific American,* 292 (6).
- Merck & Co., (5 Nov 2004). *Response to Article by Juni et al. Published in The Lancet on Nov. 5. (http://www.merck.com/statement_2004_1105/lancet.pdf)* Press Release.
- Merck & Co (30 Sep 2004) Merck Announces Voluntary Worldwide Withdrawal of VIOXX. Press release [16] (http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf).
- D. M. Mukherjee, S. E. Nissen, and E. J. Topol, "Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors," Journal of the American Medical Association 186 (2001): 954–959.
- Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;**352**(11):1081-91. PMID 15713945 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15713945)
- Okie, S (2005) "Raising the safety bar--the FDA's coxib meeting." *N Engl J Med.* 2005 Mar 31;352(13):1283-5. PMID 15800221 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15800221).
- Leleti Rajender Reddy, Corey EJ. Facile air oxidation of the conjugate base of rofecoxib (Vioxx™), a possible contributor to chronic human toxicity *Tetrahedron Lett* 2005, **46**: 927. [17] (http://dx.doi.org/doi:10.1016/j.tetlet.2004.12.055)
- Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002;162:1099-104
- Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**(11):1071-80. PMID 15713944 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?

cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15713944)
- Swan SK *et al.*, Effect of Cyclooxygenase-2 Inhibition on Renal Function in Elderly Persons Receiving a Low-Salt Diet. Annals of Int Med 2000; 133:1–9
- Targum, SL. (1 Feb. 2001) Review of cardiovascular safety database. *FDA memorandum.* [18] (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf)
- Wolfe, MM et al, Gastrointestinal Toxicity of Nonsteroidal Anti-anflamattory Drugs, New England Journal of Medicine. 1999; 340; 1888-98.

External links

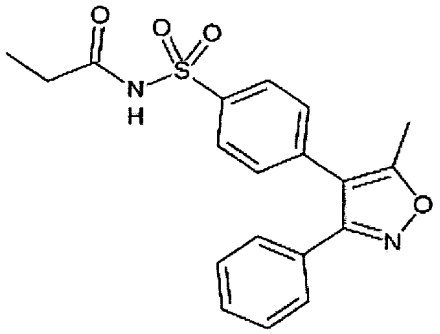
- Court TV's full coverage of the Vioxx civil trials (http://www.courttv.com/trials/vioxx/)
- Merck website on Vioxx litigation (http://www.learnaboutvioxx.com/)
- Merck's press release announcing the withdrawal (http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf) - September 30, 2004
- FDA Public Health Advisory on Vioxx (http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm)
- David Michaels. *Doubt is Their Product (http://www.sciamdigital.com/browse.cfm?sequencenameCHAR=item2&methodnameCHAR=resource_getitembrowse&interfacenameCHAR-2B35-221B-67096ED4BD9F95F7&ARTICLEID_CHAR=B3AF7D6A-2B35-221B-601840861CEDAFE1&sc=I100322)* Scientific American, June 2004, p.96-101
- JURIST, Much Pain, Much Gain: Skeptical Ruminations on the Vioxx Litigation (http://jurist.law.pitt.edu/forumy/2006/01/much-pain-much-gain-skeptical.php)
- Ted Frank, American Enterprise Institute, *The Vioxx Litigation*, Part I (http://www.aei.org/research/liability/publications/pubID.23513,projectID.23/pub_detail.asp) and Part II (http://www.aei.org/research/liability/publications/pubID.23542,projectID.23/pub_detail.asp), December 2005
- briandeer.com - Vioxx: the UK connection (http://briandeer.com/rofecoxib-index.htm)

Retrieved from "http://en.wikipedia.org/wiki/Rofecoxib"

Categories: Articles with unsourced statements since February 2007 | All articles with unsourced statements | Non-steroidal anti-inflammatory drugs | Withdrawn drugs | Merck

Parecoxib

From Wikipedia, the free encyclopedia



Parecoxib

Systematic (IUPAC) name

N-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl] sulfonyl}propanamide

Identifiers	
CAS number	202409-33-4 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=202409-33-4&rn=1)
ATC code	M01AH04 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=M01AH04)
PubChem	119828 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=119828)
Chemical data	
Formula	$C_{19}H_{18}N_2O_4S$
Mol. weight	370.422 g/mol
Pharmacokinetic data	
Bioavailability	100%
Protein binding	98%
Metabolism	Hepatic to valdecoxib and propionic acid CYP extensively involved (mainly CYP3A4 and 2C9)
Half life	22 minutes (parecoxib) 8 hours (valdecoxib)
Excretion	Renal (70%, metabolites)
Therapeutic considerations	
Licence data	EU (http://www.emea.europa.eu/humandocs/Humans/EPAR/Dynastat/Dynastat.htm)
Pregnancy cat.	Not recommended
Legal status	POM(UK)
Routes	Intravenous and intramuscular

Parecoxib is an injectable prodrug of valdecoxib. It is marketed as **Dynastat** in the European Union.

External links

- Links to external chemical sources

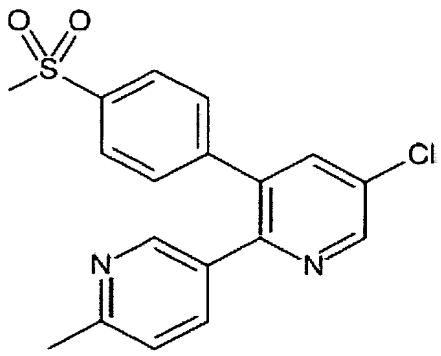
Retrieved from "http://en.wikipedia.org/wiki/Parecoxib"

Categories: Non-steroidal anti-inflammatory drugs | Prodrugs | Pharmacology stubs

Etoricoxib

From Wikipedia, the free encyclopedia

Etoricoxib (brand name **Arcoxia®** worldwide; also **Algix®** and **Tauxib®** in Italy;) is a new COX-2 selective inhibitor from Merck & Co. Doses are 60 to 120 mg/day. Currently is approved in more than 60 countries worldwide but not in the US, where the Food and Drug Administration (FDA) required



Etoricoxib

Systematic (IUPAC) name

5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

Identifiers	
CAS number	202409-33-4 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=202409-33-4&rn=1)
ATC code	M01AH05 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=M01AH05)
PubChem	123619 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=123619)
Chemical data	
Formula	$C_{18}H_{15}N_2ClO_2S$
Mol. weight	358.842 g/mol
Pharmacokinetic data	
Bioavailability	100%
Protein binding	92%
Metabolism	Hepatic, CYP extensively involved (mainly CYP3A4)
Half life	22 hours
Excretion	Renal (70%) and fecal (20%)
Therapeutic considerations	
Pregnancy cat.	Not recommended
Legal status	POM(UK)
Routes	Oral

additional safety and efficacy data for etoricoxib before it will issue approval. Current therapeutic indications are: treatment of rheumatoid arthritis, osteoarthritis, chronic low back pain, gout, and ankylosing spondylitis, acute pain. Note that approved indications differ country by country.

Like any other COX-2 selective inhibitor **Etoricoxib** selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduce prostaglandins (PGs) generation from arachidonic acid. Among the different functions exerted by PGs, it should be highlighted their role in the inflammation cascade. COX-2 selective inhibitor (aka "COXIB") showed less marked activity on type 1 cycloxigenase compared to traditional non-steroidal anti-inflammatory drugs (NSAID). This reduced activity is the cause of reduced gastrointestinal toxicity, as demonstrated in several large clinical trials performed with different COXIB (see below links on NEJM and The Lancet).

Some clinical trials and meta-analysis showed that treatment with *COXIB* lead to increased incidence of cardiovascular adverse events compared to placebo. Because of these results, some molecules were withdrawal from the market (rofecoxib, september 2004 and valdecoxib april 2005). In addition FDA and EMEA, respectively USA and European Community Health Authorities started a revision process of entire COX-2 inhibitors and NSAID classes.

FDA concluded its revision on April 6, 2005: final document can be found at:
http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf

EMEA concluded its revisione on June 27, 2005: final document can be found at:
http://www.emea.europa.eu/pdfs/human/press/pr/20776605en.pdf

External links

- European Medicine Evaluation Agency (EMEA) - Homepage (http://www.emea.eu.int/) - [1] (http://www.emea.eu.int/Cox2inhibitors.htm)
- US Food and Drug Administration (FDA) - Homepage (http://www.fda.gov/) - [2] (http://www.fda.gov/cder/drug/infopage/COX2/default.htm)
- (VIGOR study on The New England Journal of Medicine - NEJM) (http://content.nejm.org/cgi/content/abstract/343/21/1520)
- (TARGET study on The Lancet) (http://www.thelancet.com/journals/lancet/article/PIIS0140673604168931/abstract)
- (MEDAL study on The Lancet) (http://www.thelancet.com/journals/lancet/article/PIIS0140673606696669/abstract)

- Links to external chemical sources

Retrieved from "http://en.wikipedia.org/wiki/Etoricoxib"

Categories: Non-steroidal anti-inflammatory drugs | Pharmacology stubs

Valdecoxib

From Wikipedia, the free encyclopedia

Valdecoxib is a prescription drug used in the treatment of osteoarthritis, rheumatoid arthritis, and painful menstruation and menstrual symptoms. It is classified as a nonsteroidal anti-inflammatory drug, or NSAID, and should not be taken by anyone allergic to these types of medications.

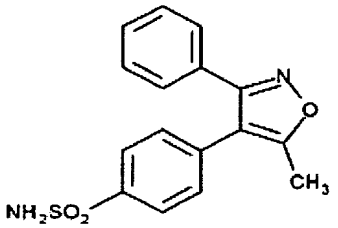
Valdecoxib was manufactured and marketed under the brand name **Bextra** by G. D. Searle & Company. It was available by prescription in tablet form until 2005, when it was removed from the market due to concerns about possible increased risk of heart attack and stroke.

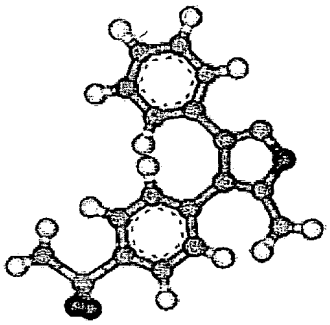
Uses

Since its registration, Bextra was prescribed for pain associated with arthritis, menstrual discomfort, and other ailments.

Side-effects and withdrawal

On April 7, 2005, Pfizer withdrew Bextra from the U.S. market on recommendation by the FDA, citing an increased risk of heart attack and stroke and also the risk of a serious, sometimes fatal, skin reaction.





Valdecoxib

Systematic (IUPAC) name

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

Identifiers

CAS number	181695-72-7 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=181695-72-7&rn=1)
ATC code	M01AH03 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=M01AH03)
PubChem	119607 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=119607)
DrugBank	APRD00183 (http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00183)

Chemical data

Formula	$C_{16}H_{14}N_2O_3S$
Mol. weight	314.364 g/mol

Pharmacokinetic data

Bioavailability	83%
Protein binding	98%
Metabolism	Hepatic (CYP3A4 and 2C9 involved)
Half life	8 to 11 hours

Excretion	Renal
Therapeutic considerations	
Pregnancy cat.	C(AU) May cause premature closure of the ductus arteriosus
Legal status	**Withdrawn** in U.S., EU, Canada & parts of Asia
Routes	Oral

This was a result of recent attention to prescription NSAIDs, such as Merck's Vioxx. Other reported side-effects were angina and Stevens-Johnson syndrome.

Pfizer first acknowledged cardiovascular risks associated with Bextra in October of 2004. The American Heart Association soon after was presented with a report indicating patients using Bextra while recovering from heart surgery were 2.19 times more likely to suffer a stroke or heart attack than those taking placebos.

Recently in a large study published in JAMA 2006, Valdecoxib appears less adverse for renal (kidney) disease and heart arrhythmia compared to Vioxx, however elevated renal risks was slightly suggested. Systematic review of adverse renal and arrhythmia risk of celecoxib and other COX-2 inhibitors, in JAMA 2006 (http://www.cox2drugreview.org/)

External links

- FDA Alert on Bextra withdrawal (http://www.fda.gov/cder/drug/InfoSheets/HCP/valdecoxibHCP.htm)
- Large systematic review of adverse renal and arrhythmia risk of valdcoxib and other COX-2 inhibitors, JAMA 2006 (http://www.cox2drugreview.org/)

Retrieved from "http://en.wikipedia.org/wiki/Valdecoxib"

Categories: Non-steroidal anti-inflammatory drugs | Withdrawn drugs